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Bacterial co-infection at hospital admission in patients with COVID-19

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Running title: Bacterial co-infections in COVID-19.

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Highlights

- Over 9% of patients hospitalized for COVID-19 will present a co-infection.
- Independent risk factors for co-infection were identified.
- When procalcitonin values are <0.2 ng/mL, co-infection is very rare.
- High ferritin values and oxygen saturation >94% are also uncommon in co-infection.

ABSTRACT

Objectives: We describe the current incidence and risk factors of bacterial co-infection in COVID-19 hospitalized patients.

Methods: Observational cohort study performed at Hospital Clinic of Barcelona (February 2020 - February 2021). All patients with COVID-19 admitted >48 hours, with microbiological sample collection and procalcitonin (PCT) determination within the first 48 hours were included.

Results: 1125 consecutive adults met inclusion criteria. Co-infections were microbiologically documented in 102 (9.1%) patients. Most frequent microorganisms were *S. pneumoniae* (79%), *S. aureus* (6.8%) and *H. influenzae* (6.8%). Test positivity was 1% (8/803) for blood cultures, 10.1% (79/780) for pneumococcal urinary antigen test, and 11.4% (15/132) for sputum culture. Patients with PCT higher than 0.2, 0.5, 1, and 2 ng/mL had significantly more co-infections than those with lower levels ($p=0.017$, $p=0.031$, $p<0.001$, and $p<0.001$, respectively). In multivariate analysis, oxygen saturation ≤94% (OR 2.47, CI 1.57-3.86); ferritin levels <338 ng/mL (OR 2.63, CI 1.69-4.07); and PCT higher than 0.2 ng/mL (OR 1.74, CI 1.11-2.72) were independent risk factors for co-infection at hospital admission due to COVID-19.

Conclusions: Bacterial co-infection in patients hospitalized for COVID-19 is relatively common. However, clinicians could spare antibiotics in patients with PCT values <0.2 especially with high ferritin values and oxygen saturation >94%.

Key words: COVID-19; bacterial infection; co-infection; antibiotics; SARS-CoV-2.

INTRODUCCION

On July 23rd 2021, more than 190 million people had been infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) worldwide, of whom more than 4.1 million died (WHO Coronavirus (COVID-19) Dashboard | WHO Coronavirus (COVID-19) Dashboard With Vaccination Data, n.d.). Approximately 10% of patients with COVID-19 pneumonia will require hospital admission for different clinical complications, including hyperinflammatory response, thrombotic events, organizing pneumonia or co-infections. These complications may have clinically similar presentation, such as fever, dyspnea and/or respiratory deterioration. However, each will require a personalized therapeutic approach (Garcia-Vidal et al., 2020).

A leading challenge for physicians treating COVID-19 is deciding when antibiotics are necessary at hospital admission. In the first pandemic wave, most patients received antibiotics at disease onset, although few reports described low incidence of bacterial co-infections (Adler et al., 2020; Garcia-Vidal et al., 2021b; Lehmann et al., 2021). A year after the start of the pandemic, there are still unresolved questions with respect to both the usefulness of procalcitonin (PCT) in ruling out co-infection or the selection of clinical phenotypes or analytical patterns to identify patients at a higher risk of co-infection. Although some epidemiological changes have occurred through the different waves of the pandemic (Garcia-Vidal et al., 2021a), recent data regarding incidence and epidemiological characteristics of co-infections are lacking.

For all of these reasons, we aimed to describe the current incidence of co-infection in hospitalized patients with COVID-19 and identify factors that may help clinicians initiate or discard empirical antibiotics correctly.

PATIENTS AND METHODS

Study design and patients

This observational cohort study was performed at Hospital Clinic of Barcelona, a 700-bed university center that provides broad and specialized medical, surgical, and intensive care for an urban population of 500,000 adults (>18 years old). We retrospectively analyzed all consecutive adults hospitalized for SARS-CoV-2 infection between 19 February 2020 and 24 February 2021 who met all of these criteria: 1) hospital admission for more than 48 hours; 2) microbiological samples collected within the first 48 hours at hospital admission; 3) serum creatinine lower than 2 mg/dL; and 4) at least one PCT determination within the first 48 hours of admission. Patients with a positive urine culture were excluded due to difficulties in assessing the clinical relevance of urinary infections retrospectively. All patients had a confirmed diagnosis of COVID-19 by real-time polymerase chain reaction (RT-PCR) performed in nasal and oropharyngeal throat-swab, and/or by fulfilment of clinical diagnostic criteria for SARS-CoV-2 during the first peak of the pandemic (March-April 2020). The suspected bacterial co-infection was defined based on a positive microbiological sample with clinical significance within the first 48 hours of admission.

Our group previously published a work about bacterial co-infections in the first year of SARS-CoV-2 pandemics (Garcia-Vidal et al., 2021b). In the present study we focus on those episodes in which active co-infection screening was performed. The primary outcome of this study was to determine the incidence of bacterial co-infection in this selected population of patients with COVID-19. Secondary outcomes were: i) To evaluate the yield of the different microbiological tests; ii) To evaluate the role of PCT at different thresholds to identify patients with co-infection; and iii) To identify independent risk factors for co-infection at hospital admission.

The Institutional Ethics Committee of Hospital Clinic of Barcelona approved the study and due to the nature of the retrospective data review, waived the need for informed consent from individual patients (HCB/2020/0273).

Data collection and clinical assessment

High-quality data on demographic characteristics, clinical signs, laboratory tests, microbiological results (blood cultures, respiratory samples and urinary antigen tests), treatments, and outcomes (ICU admission, need for mechanical ventilation and mortality) were collected directly from electronic health records using an intelligent system to retrieve high-quality data from EHRs (SILDv1.0 system, S34M@) as described elsewhere (Garcia-Vidal et al., 2019). All patients with positive microbiological results were reviewed by one of our researchers (CGV, PP, EMG or LLG) for clinical significance assessments.

Definitions

Clinical diagnostic criteria for SARS-CoV-2 included clinical symptoms (fever, respiratory tract symptoms, myalgia, diarrhea, and smell or taste aberrancies); laboratory findings (lymphopenia, as well as elevated levels of aminotransaminase, lactate dehydrogenase, inflammatory markers such as ferritin and C-reactive protein, and D-dimer); and chest x-ray or computed tomography (CT) suggestive of COVID-19 with no other etiology that would explain clinical presentation in its entirety.

Microbiological methods

We considered bacterial infections as significant when one or more of the following criteria were met: 1) positive blood culture with a non-contaminant bacteria; 2) positive cultures obtained from good-quality sputum (<10 squamous cells and >25 leukocytes per low-power field) and/or pleural fluids; and 3) positive urinary antigen test.

Additionally, detection of *Streptococcus pneumoniae* urinary antigen was done by a rapid immunochromatographic assay (NOW Assay; Binax Inc, Portland, ME). STANDARDTM F for serogroup 1 *Legionella pneumophila* was performed in urine samples. Blood samples were processed using either a BACTEC 9240 system (Becton–Dickinson Microbiology Systems, Franklin Lakes, NJ, USA) or BacTAlert (BioMérieux SA, Marcy L'Etoile, France) for a 5-day incubation period.

Statistical analysis

Categorical variables were described using the absolute number and percentage, while continuous variables were presented using the median and interquartile range (IQR). Categorical variables were compared using either a chi-squared (χ^2) test or Fisher´s exact test when appropriate, and medians with the Mann-Whitney U test. Statistical significance was defined as P value <0.05. Factors associated with co-infection were evaluated by univariate and multivariate analysis, with the multivariate analysis including all significant variables (P<0.05) from the univariate analysis. Diagnostic accuracy of PCT was assessed by calculating sensitivity, specificity, negative predictive value and positive predictive value of different PCT cut-off values. A two-tailed $P < 0.05$ was considered as significant. Analyses were performed with Microsoft SPSS-PC+, version 22.0 (SPSS, Chicago, IL, USA).

RESULTS

Description of overall population and co-infection

During the study period, we assessed 1125 consecutive adults who met the inclusion criteria. Figure 1 shows the flowchart of patients' inclusion. Epidemiological and clinical characteristics of these patients are summarized in Table 1. Attending physicians ordered microbiological test comprising one or more of the following: blood cultures in 803 patients, in whom 8 (1%) were positive; pneumococcal urinary antigen tests in 780 patients, in whom 79 (10.1%) were positive; legionella urinary antigen tests in 776 patients, all of which were negative; and cultures of good quality sputum in 132 patients, of whom 15 (11.4%) were positive.

Co-infections were microbiologically documented in 102 (9.1%) patients, representing the 3.2% of the whole cohort (including those patients not meeting the inclusion criteria). Co-infection epidemiology is detailed in Table 2. The most frequent microorganisms found were: *S. pneumoniae* in 81 patients (representing 79% of patients with co-infections, and causing 7.2% of co-infections in the overall cohort); *Staphylococcus aureus* in 7 patients (6.8%; 0.6%), and *Haemophilus influenzae* in 7 patients (6.8%; 0.6%).

Relationship between PCT levels and co-infection

Median PCT levels were similar between patients with co-infection and those without co-infection (0.12 ng/mL; Interquartile range 0.06-0.34 vs 0.11 ng/mL, IQR 0.06-0.22; p=0.534). Specifically, median PCT was higher in patients with bacteremia when compared with those without bacteremia (0.48 ng/mL, IQR 0.27-36.7 vs 0.11 ng/mL, IQR 0.06-0.23; p=0.019). No significant differences were found in median PCT values between patients with either positive pneumococcal urinary antigen or positive sputum culture and those with negative results.

Patients with PCT higher than 0.2, 0.5, 1, and 2 ng/mL had significantly more co-infections than those with lower levels (p=0.017, p=0.031, p<0.001, and p<0.001, respectively). Table 3 details the sensitivity, specificity, negative and positive predictive value of PCT cut-off values of 0.2, 0.5, 1, and 2 ng/mL for co-infection detection.

Predictors of COVID-19 co-infection

In the univariate analysis, patients with co-infection at onset presented with: i) a higher respiratory rate (20 rpm median value versus 22; p=0.05); ii) lower oxygen saturation (95% versus 94%; p=0.012); iii) decreased ferritin levels (602 ng/mL median value versus 338 ng/mL; p=0.012); and iv) PCT higher than the cut-off value of 0.2 ng/mL (18.6% vs 11.3%; p=0.031). No other differences were documented when compared with patients without co-infection.

In the multivariate analysis, oxygen saturation equal or lower than 94% (OR 2.47, CI 1.57-3.86); ferritin levels lower than 338 ng/mL (OR 2.63, CI 1.69-4.07); and PCT higher than the cut-off value of 0.2 ng/mL (OR 1.74, CI 1.11-2.72) were independent risk factors for co-infection at hospital admission due to COVID-19. The goodness-of-fit of the multivariate model was assessed using the Hosmer-Lemeshow test (0.387). The discriminatory power of the score, as evaluated by the area under the receiver operating characteristic curve, was 0.677 (95% CI, 0.619-0.734), demonstrating a moderate ability to predict co-infection.

DISCUSSION

The results obtained from of our study demonstrate that co-infection was relatively frequent (approximately 10%) in hospitalized patients with COVID-19 during the first year of pandemic. We identify that those patients with oxygen saturation equal or lower than 94% who had lower ferritin levels and PCT higher than the cut-off value of 0.2 ng/mL had more frequently co-infection. The PCT cut-off value of 0.2 ng/mL has a high NPV to rule out co-infection.

Prior studies had reported lower incidence of co-infection in this population, ranging between 2% and 6% (Adler et al., 2020; Garcia-Vidal et al., 2021b; Lehmann et al., 2021). However, some important, methodological differences among the studies should be noted. In contrast with these previous studies, the current study only includes patients for whom microbiological tests had been ordered to rule out this complication. Moreover, this study describes a series of patients admitted to the hospital for COVID-19 during the first, full year of the pandemic. This aspect of the study differs from other studies, which included patients from only the first few months. This point may be important for different reasons. For example, we may have improved the diagnostic approaches used for co-infection detection over the months. Also, a change in patient characteristics over time could have an impact on the risk of co-infection. Some researchers warned of a potential increase in pneumococcal colonization among adults as a result of close contact with children (Almeida et al., 2021). It would be logical, therefore, to believe that following at-home confinements, contact between adults and children may have been especially close, potentially increasing pneumococcal colonization of the elderly.

Our study documented that both the pneumococcal urinary antigen test and the sputum culture comprise two of the most important tests when it comes to ruling out co-infections in patients with COVID-19 at hospital admission. Both techniques may provide quick-time results and contribute to improved decision-making processes regarding antibiotic use among treating physicians. While our study recorded very infrequent use of sputum culture, when performed, it was able to diagnose 11% of patients, nonetheless. Currently, *S. aureus* and *H. influenzae* co-infections cannot be diagnosed by other microbiological techniques. Therefore, the incidence of such co-infections could be underestimated in most cohorts of patients with COVID-19. We recommend increasing the use of Gram staining and sputum culture in all patients with productive sputum arriving to the hospital, which could provide valuable, insightful information within a few minutes. On the other hand, as has been done in bacterial pneumonia management, clinicians could consider not performing blood cultures, at least in patients with a PCT lower than 0.5 ng/ml (Falguera et al., 2009). In our view, due to low frequency of the pathogen, it does not make sense to perform *Legionella* urinary antigen routinely at onset.

The role of PCT in ruling out co-infections in patients hospitalized with COVID-19 remains a controversial topic. Some prior studies analyzing this issue included a very low number of patients and had several methodological limitations (Heer et al., 2021;

Malinverni et al., 2021; Pink et al., 2021). May et al. retrospectively analyzed the role of PCT in diagnosing co-infection in a larger cohort of 2443 patients admitted with COVID-19 (May et al., 2021). However, there are important differences between their study and ours. Firstly, May et al. included patients in whom no microbiological tests had been performed to rule out bacterial infections as patients without co-infection. Secondly, they also included patients with positive urine cultures as patients with co-infection. In our view, it is difficult to retrospectively assess the relevance of clinical infection in patients with positive urine cultures. It is even more challenging to associate urine infections with COVID-19. Finally, the authors do not report the incidence of renal failure in the study cohort. In our experience, renal insufficiency was associated with difficult-to-assess PCT values; consequently, we excluded these patients from our work (El-sayed et al., 2014; Grace and Turner, 2014). Yet, despite all of these methodological differences, both those authors and we similarly conclude that PCT has limited utility in diagnosing bacterial co-infections. Importantly, nonetheless, PCT may play a role in ruling out this complication. Other authors have described that withholding antibiotics in patients with COVID-19 and a PCT cut-off value lower than 0.25 ng/ml may prove safe (Williams et al., 2021).

In our study, we more frequently identified bacterial co-infections among patients with oxygen saturation equal or lower than 94%; ferritin levels lower that 338 ng/mL; and PCT higher than a cut-off value of 0.2 ng/mL. The relationship between low ferritin values and bacterial co-infection may be attributable to the fact that patients with COVID-19 with high ferritin levels have hyperinflammatory syndrome more frequently as a cause of hospital admission.

Our study does have some limitations that should be acknowledged. First, not all patients had sputum culture, urinary antigen test and blood cultures performed at hospital admission. Therefore, under-diagnosis of some co-infections may have occurred. Secondly, hospital's protocol regarding patient care and COVID-19 recommends that clinicians order microbiological tests to rule out co-infection and measure PCT at hospital admission. However, our selection of patients, for whom these tests were ordered, may then also bias the frequency of co-infections. Additionally, we decided to exclude urinary cultures, as these are commonly difficult to evaluate in otherwise asymptomatic patients, and because urinary tract co-infection is not expectable in patients with pneumonia. However, this introduced another bias and could have influenced the final study result. Lastly, as this study was conducted at a single center, frequency and microbiological epidemiology may vary according to different geographical contexts. The strengths of this study include the large number of cohort subjects and the clear, complete collection of clinical and microbiological data for optimal evaluation of factors related with co-infection, especially the role of PCT in ruling out this complication.

To conclude, bacterial co-infection is a relatively common COVID-19 complication diagnosed in 10% of hospitalized adults. Our results suggest that avoiding the use of antibiotics in patients with COVID-19 and PCT values below 0.2 especially with high ferritin values and oxygen saturation greater than 94%, may constitute a wise approach as it relates to making decisions related to antibiotic use at admission. Clinicians should perform pneumococcal urinary antigen test, Gram staining and sputum cultures in all patients when possible. The need for antibiotics should then be re-evaluated within the first 24 hours of these results.

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

CG-V has received honoraria for talks on behalf of Gilead Science, MSD, Novartis, Pfizer, Janssen, Lilly as well as a grant from Gilead Science and MSD. AS has received honoraria for talks on behalf of Merck Sharp and Dohme, Pfizer, Novartis, Angellini, as well as grant support from Pfizer. PC has received honoraria for talks on behalf of Merck Sharp and Dohme, Pfizer, Gilead and Alexion. JM has received honoraria for talks on behalf of Merck Sharp and Dohme, Pfizer, Novartis and Angellini. PP-A has received honoraria for talks on behalf of Merck Sharp and Dohme, Gilead, Lilly, ViiV Healthcare and Gilead Science.

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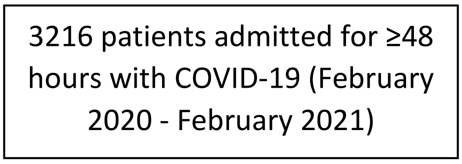

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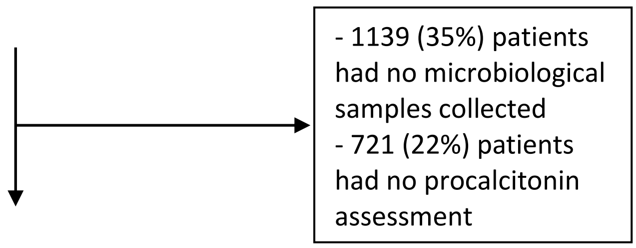
Figure 1. Flowchart of patients' inclusion.



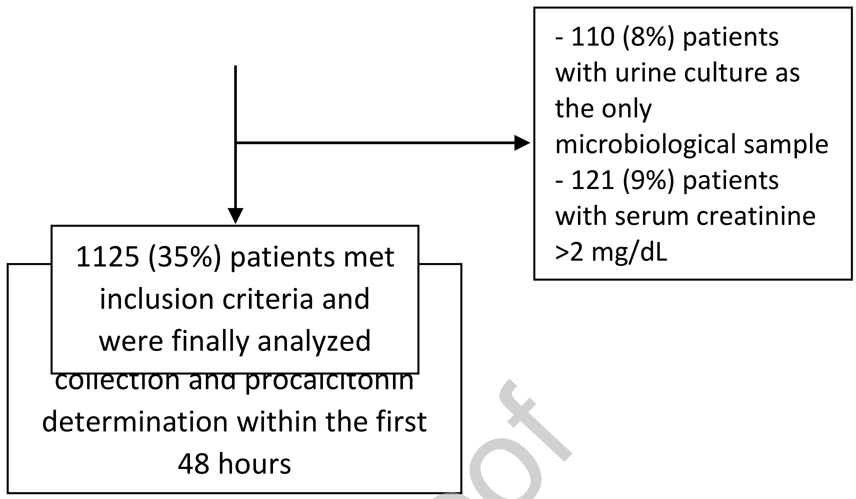


Table 1. Main epidemiological and clinical characteristics of patients

	All patients (n=1125)	Patients without co-infection (n=1023)	Patients with co-infection (n=122)	p- value
Patient characteristics				
Age-Median (IQR), in years	64 (54-75)	64 (54-75)	64.5 (54.8-76)	0.955
Male sex, n (%)	700 (62.2)	645 (63.1)	55 (53.9)	0.068
Comorbidities (%)				
Hypertension	480 (42.7)	442 (43.2)	38 (37.3)	0.247
Diabetes mellitus	198 (17.6)	179 (17.5)	19 (18.6)	0.775
Chronic heart disease	250 (22.2)	223 (21.8)	27 (26.5)	0.279
Chronic lung disease	281 (25)	248 (24.2)	33 (32.4)	0.071
Hematological malignancy	71 (6.3)	60 (5.9)	11 (8.8)	0.235

Chronic liver disease	86 (7.6)	77 (7.5)	9 (8.8)	0.638
Solid neoplasm	162 (14.4)	144 (14.1)	18 (14.7)	0.862
Vital signs at admission; Median (IQR)				
Temperature (ºC)	37.3 (36.6-38.0)	37.3 (36.6-38.0)	37.2 (36.4-37.8)	0.690
Respiratory rate (bpm)	20 (18-25)	20 (18-24)	22 (18-28)	0.423
Oxygen saturation (by pulseoximetry)	95 (93-97)	95 (93-97)	94 (92-96)	0.064
Laboratory values at admission; Median (IQR)				
Ferritin (ng/mL)	589 (269-1121.75)	602 (276-1134)	338 (202-1078)	0.055
C-RP (mg/dL)	8.9 (4.75-15.4)	9.0 (4.7-15.4)	9.9 (4.8-16.6)	0.597
D-dimer (ng/mL)	700 (400-1300)	700 (400-1300)	700 (400-1600)	0.233
LDH (U/L)	322 (257-409)	322 (257-405)	336 (241-438)	0.827
Lymphocyte count (cells/mm^3)	0.8 (0.6-1.1)	0.8 (0.6-1.1)	0.8 (0.5-1.2)	0.927
PCT (ng/mL)	0.11 (0.6-0.23)	0.11 (0.06-0.22)	0.12 (0.06-0.34)	0.534

*Abbreviations. IQR=interquartile range; bpm=breaths per minute; C-RP=C-reactive protein; LDH=lactate dehydrogenase; PCT=procalcitonin.

Table 2. Epidemiology of bacterial co-infections at COVID19 admission.

	n=102 (%)
Respiratory co-infection diagnosed by pneumococcal urinary antigen	79

Respiratory co-infection diagnosed by sputum culture	15[a]
S. pneumoniae	4[b]
P. aeruginosa	2
S. aureus	5
K. pneumoniae	1
H. influenzae	6
Bacteremia	8
E. coli	3
S. aureus	3
P. aeruginosa	1
H. influenzae	1

[a]Three patients had a positive polymicrobial sputum culture.

[b]In three of the four patients with positive *S. pneumoniae* in the sputum culture, pneumococcal urinary antigen was not performed. In the other patient, urinary antigen was negative.

Table 3. Sensitivity, specificity, predictive negative value and predictive positive value of different PCT cut-offs for co-infection detection.

	PCT ≥0.20 ng/ml	PCT ≥0.50 ng/ml	PCT ≥1 ng/ml	PCT ≥2 ng/ml
Sensitivity	0.40	0.19	0.14	0.14
Specificity	0.71	0.89	0.95	0.97
Negative predictive value	0.92	0.92	0.92	0.92
Positive predictive value	0.12	0.14	0.21	0.34

*Abbreviations. PCT=procalcitonin.